REMARKS

Upon entry of the amendments submitted herewith, claims 38-39, 41-48, 53-54, 65, 68-79, and 81-87 will be pending in this application.

Applicants have canceled claims 40, 55, and 80, and amended claims 38, 47, and 53, to remove non-elected subject matter. Applicants reserve their right for rejoinder of additional species as detailed in the previous Office Action.

Applicants have amended claims 68 and 82-84 to more clearly describe the weight average molecular weight of the recited polyvinylpyrrolidone. The claim dependency of claims 81-84 has been amended in view of the cancelation of claim 80.

Applicants respectfully submit that the claim amendments submitted herewith do not add any new matter within the meaning of 35 U.S.C. §132 to the application.

Accordingly, entry of the above amendments is respectfully requested.

1. Rejection of claims 68 and 80-84 under 35 U.S.C. §112, 2nd paragraph

The Official Action states that claims 68 and 82-84 are rejected under 35 U.S.C. §112, 2nd paragraph, as being indefinite for allegedly not properly referring to the recited polymers as having an average molecular weight, or which type of average molecular weight is referred to for the recited molecular weights of polyvinylpyrrolidone. Claim 80, and claims 81-84 which depend thereon, is allegedly indefinite for reciting the process "which is a tablet."

RESPONSE

Regarding the rejection of claims 68 and 82-84, applicants respectfully point out to the Examiner that claims 68 and 82-84 have been amended to recite "the weight average" molecular weight for the polyvinylpyrrolidone. Support for this amendment is found, for example, in the specification at page 7, first full paragraph. Thus, the basis for this rejection is moot. Further, one of ordinary skill in the art would understand from the various manufacturers' information, and applicants' specification, regarding Kollidon 90 (K90) that this polyvinylpyrrolidone has the weight average molecular weight recited in the claims.

Regarding claim 80, applicants canceled claims 40, 55, and 80, and amended claims 38, 47, and 53, to remove non-elected subject matter reciting "pellets". Applicants reserve their right for rejoinder of additional species as detailed in the previous Office Action. The claim dependency of claims 81-84 has been amended so they amend from claim 47 rather than canceled claim 80.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw these rejections.

2. Rejection of Claims 38, 39, 41, 45-48, 65, 69, 71-81, and 87 under 35 U.S.C. §103(a)

The Official Action states that claims 38, 39, 41, 45-48, 65, 69, 71-81, and 87 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Rennard, et al. (US Published Application No. 20030018071) in combination with Ghebre-Sellassie et al. (US Patent No. 6,667,362) and Remington: The Science and Practice of Pharmacy, 1995.

RESPONSE

Applicants respectfully traverse this rejection. The cited references do not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The Examiner has failed to establish a *prima facie* case of obviousness against the presently rejected claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. _ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*,

165 USPQ 494, 496 (C.C.P.A. 1970).

The primary Rennard et al. reference teaches the combination of certain PDE4 inhibitors with a pharmaceutical carrier. The Rennard reference does not teach each and every element of the presently pending claims. In particular, it does not teach a process for producing a dosage form using PVP in any amount. Furthermore, Rennard makes no mention of solubility of any PDE4 inhibitors, including roflumilast, and makes no mention of whether or not drug solubility is an issue for preparing a formulation.

The secondary Ghebre-Sellassie, et al. reference teaches a method for preparing a drug-PVP dosage form using only "solvent-free" PVP. See Example I, and claim 1. The Ghebre-Selassie method teaches spraying the required plasticizer/solubilizer on a solvent-free complex of PVP and active drug to form granules having a drug-PVP core coated with plasticizer/solubilizer. See Example I, and claim 1. There is no suggestion of using an aqueous system alone with PVP to prepare a low water soluble drug formulation.

The Remington reference discusses the use of PVP as a binder for preparation of dosage forms by using either aqueous or alcoholic solutions. Page 1618, bottom of column 1. The Remington reference also generally discusses methods of producing dosage forms, including a "new method for granulating" called fluid-bed granulation. Page 1625, top of column 2. However, the Remington reference neither recognizes the need for nor discloses the possibility of increasing bioavailability of low solubility drugs using an aqueous process for granulation. Furthermore, Remington neither teaches nor suggests the possibility of formulating low solubility drugs using aqueous PVP.

Thus, a person of ordinary skill would not be motivated, upon reading the Remington's reference, to combine it with the teachings of the other references to obtain a

process for producing a dosage form of a low soluble drug comprising granulating with aqueous PVP.

Applicants point out that the current process claims comprise granulating with "aqueous PVP" while the Ghebre-Selassie method teaches use of only "solvent-free" PVP in the core of the granules and granulating with a plasticizer/solubilizer solution. See col. 4, lines 9-34, and Example I. The Ghebre-Selassie method does not teach or suggest adding PVP to the plasticizer/solubilizer spraying solution. Moreover, the Ghebre-Selassie method diverges greatly from the present claims by requiring granulation with a plasticizer/solubilizer composition to interact with the low solubility drug formulation to overcome the problem of formulating a low solubility drug in combination with solvent-free PVP.

Contrary to the teachings of Ghebre-Selassie, Applicants have overcome the problem of formulating a composition containing a specific low solubility drug by granulating with aqueous PVP. Thusly, Ghebre-Selassie teaches away from Applicants claimed process of granulating with aqueous PVP because Ghebre-Selassie (1) only uses "solvent-free" PVP, (2) uses solvent-free PVP only as the drug carrier in the core, and (3) requires granulation of the drug-PVP dry component core by granulating with a plasticizer/solubilizer solution. In contrast, Applicants claimed process (1) only uses aqueous PVP, and (2) requires granulating the drug core with an aqueous solution of PVP, which aqueous solution is deposited on the core. One of skill in the art reading Ghebre-Selassie's solvent free PVP core method granulated with a plasticizer/solubilizer solution does not provide motivation or predictable guidance for devising the claimed method of granulating with aqueous PVP.

Neither does the combination of references correct these deficiencies, and fails to teach a process for producing a dosage form of a low solubility drug comprising granulating a drug core with aqueous PVP. The combination of references does not teach or suggest a process for preparing a low solubility drug formulation using an aqueous PVP formulation.

In addition, in the last obviousness rejection below, the Examiner cites Chiou et al., "Pharmaceutical Applications of Solid Dispersion Systems", 1971, as art relevant to drug-PVP formulations. Applicants note that Chiou teaches that "[d]ue to the chemical instability of polyvinylpyrrolidone to heat and its high melting point..., the drug-polyvinylpyrrolidone solid dispersions can only be prepared by the solvent method. Polyvinylpyrrolidone is also soluble in a variety of organic solvents, an advantage in accommodating various drugs which possess limited solubility properties." Page 1292, first column, last paragraph, emphasis added. Accordingly, Chiou clearly teaches away from Applicants' claimed method of making a low solubility drug-PVP solid formulation using aqueous PVP.

Moreover, a person of ordinary skill reading Chiou in combination with Rennard, Ghebre-Sellassie, and Remington would have reason to understand that drug-PVP solid dispersions could only be prepared using (1) the solvent method of Chiou or (2) the solvent-free PVP method of Ghebre-Selassie requiring a plasticizer/solubilizer granulating solution. For the same reasons, one of ordinary skill would have had no reasonable expectation of successfully preparing a low solubility drug formulation using aqueous PVP.

Furthermore, *in arguendo*, even if the combination of references suggests an invitation to try combining disparate elements selectively chosen in hindsight from the cited documents to formulate (1) a low solubility drug in (2) a fluid bed granulator in combination

with (3) PVP as a binder and (4) the PVP in aqueous solution, there is no indication in the cited documents or within the knowledge of one of ordinary skill in the art at the time of invention that this combination of components would have a reasonable expectation of successfully preparing a low solubility drug complex by granulating with aqueous PVP. Furthermore, there is no indication that this combination of processes would predictably and successfully produce a low solubility drug formulation that has enhanced bioavailability of the water insoluble drug.

Applicants point to the data in the specification at page 20, Figure 1, and in the expert's declaration submitted on April 27, 2007. The data shows that the dosage forms produced by the presently claimed processes comprising roflumilast granulated with aqueous PVP lead to higher serum levels of roflumilast in the blood more quickly than the roflumilast dosage forms not granulated with PVP.

Moreover, in the specification at page 11, Applicants describe that "[i]t has surprisingly been found that dosage forms of the invention ... have similar advantageous properties in relation to the bioavailability of the PDE 4 inhibitor whose solubility is slight as do dosage forms produced by first producing solid solutions of PVP and PDE 4 inhibitor." Thus, at the time of invention, there was no reasonable or predictable expectation that one of ordinary skill in the art reading the cited references would have successfully identified that the combination of PVP with a PDE 4 inhibitor produced by granulating with aqueous PVP would achieve the surprising and advantageous properties discovered by Applicants. Furthermore, routine experimentation would not have identified nor predicted these surprising and advantageous properties of the low solubility PDE4 inhibitor formulation granulated with aqueous PVP according to the claims.

Accordingly, the combination of art cited by the Examiner does not teach or suggest each and every element of the presently claimed invention, and there is no reasonable expectation of successfully combining the elements selectively chosen by the Examiner in hindsight to practice the claimed subject matter.

Therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 38, 39, 41, 45-48, 65, 69, 71-81, and 87 under 35 USC §103(a).

3. Rejection of Claims 68 and 82-84 under 35 U.S.C. §103(a)

The Official Action states that claims 68 and 82-84 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Rennard in combination with Ghebre-Sellassie and Remington, and further in view of US Patent No. 5,262,171 to Login et al.

RESPONSE

Applicants respectfully traverse this rejection. The references of record do not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The Examiner has failed to establish a *prima facie* case of obviousness against the presently rejected claims.

For the sake of brevity, the arguments set forth above in section 1 are incorporated herewith as they pertain to the teachings of the Rennard, Ghebre-Sellassie, and Remington references, and including the teaching away of Chiou. The additional Login reference does not remedy the deficient teachings of the aforementioned combination of references and, thus, cannot establish a *prima facie* case of obviousness against the presently rejected claims.

The Examiner asserts that "Login teaches that PVP suitable for use in tablets has [sic] is graded as K-30 to K-120 molecular weight." The Login reference relates to methods for synthesizing PVP having different polymer length and degree of cross linking. Login provides examples of pharmaceutical tablets prepared using an active ingredient, such as acetaminophen, and 1% and 2% PVP by weight. See example 7, col. 8, lines 57-61. There is no indication if the tablets are 98-99% acetaminophen, or if other fillers or bonders are also employed. Furthermore, there is no indication of how the tablets were physically made. Login does not teach or suggest using an aqueous PVP to prepare a low solubility drug formulation.

Thus, a person of ordinary skill would not be motivated, upon reading the Login reference, to combine it with the teachings of the other references to obtain a process for producing a dosage form of a low soluble drug comprising granulation by spraying aqueous PVP.

As such, applicants respectfully request that the Examiner reconsider and withdraw the rejection.

4. Rejection of Claims 42-44, 53, 54, 85, and 86 under 35 U.S.C. §103(a)

The Official Action states that claims 42-44, 53, 54, 85, and 86 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Rennard in combination with Ghebre-Sellassie and Remington, and further in view of Chiou et al., "Pharmaceutical Applications of Solid Dispersion Systems", 1971.

RESPONSE

Applicants respectfully traverse this rejection. The references of record do not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The Examiner has failed to establish a *prima facie* case of obviousness against the presently rejected claims.

For the sake of brevity, the arguments set forth above in section 1 are incorporated herewith as they pertain to the teachings of the Rennard, Ghebre-Sellassie, and Remington references. The additional Chiou reference does not remedy the deficient teachings of the aforementioned combination of references and, thus, cannot establish a *prima facie* case of obviousness against the presently rejected claims.

The Examiner asserts that Chiou "teaches the use of solid dispersions to increase the availability of poorly water soluble drug (1281-1283)." The Chiou reference relates generally to the preparation, use, and characterization of solid dispersion systems for pharmaceutical applications. Chiou describes the three methods known for preparing solid dispersion formulations of drugs: the melting method; the solvent method; and the melting-solvent method. Pages 1283-1284. Chiou describes how drug-polyethylene glycol solid dispersions exemplify the melting method or melting-solvent method. Pages 1283-1284.

Chiou also describes several drug-PVP solid dispersions that can be made with the solvent method. Page 1283. Chiou does not teach or suggest using an aqueous PVP to prepare a low solubility drug formulation. Most importantly, Chiou does teach that "[d]ue to the chemical instability of polyvinylpyrrolidone to heat and its high melting point..., the drug-polyvinylpyrrolidone solid dispersions can only be prepared by the solvent method. Polyvinylpyrrolidone is also soluble in a variety of organic solvents, an advantage in

accommodating various drugs which possess limited solubility properties." Page 1292, first column, last paragraph, emphasis added. Accordingly, Chiou clearly teaches away from Applicants' claimed method of making a low solubility drug-PVP solid formulation using aqueous PVP. First, by teaching that drug-PVP solid dispersions can only be prepared by the solvent method. And second, by teaching that PVP is soluble in a variety of organic solvents and therefore provides an advantage in accommodating various drugs which possess limited solubility properties.

Thus, Chiou impliedly suggests that when choosing a solvent for preparing a drug-PVP solid dispersion, one of skill in the art should choose a PVP-solvent that matches the solubility of the selected drug. Therefore, in order to gain this advantage taught by Chiou, one of skill in the art would have been motivated to combine a low solubility drug and PVP with one of a variety of non-aqueous organic solvents of solubility similar to the drug. Accordingly, one of skill in the art would have been motivated to deliberately not combine a low water solubility drug with PVP in an aqueous solution. In addition, Chiou's teaching of the availability of several advantageous PVP organic solvents for selecting a suitable solvent is a further indication that one of skill would have neither predicted nor had reason to select the use of aqueous-PVP to formulate a low solubility drug.

Moreover, a person of ordinary skill reading Chiou in combination with Rennard, Ghebre-Sellassie, and Remington would have reason to understand that drug-PVP solid dispersions could only be prepared using (1) the solvent method of Chiou or (2) the solvent-free PVP method of Ghebre-Selassie requiring a plasticizer/solubilizer granulating solution. For the same reasons, one of ordinary skill would have had no reasonable expectation of successfully preparing a low solubility drug formulation using aqueous PVP.

Thus, a person of ordinary skill would not be motivated, upon reading the Chiou reference, to combine it with the teachings of the other references to obtain a process for producing a dosage form of a low soluble drug comprising spraying aqueous PVP.

As such, applicants respectfully request that the Examiner reconsider and withdraw the rejection.

5. Rejection of Claims 68 and 82-84 under 35 U.S.C. §103(a)

The Official Action states that claims 68 and 82-84 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Rennard in combination with Ghebre-Sellassie and Remington, and further in view of Hatzelmann et al., "Antiinflammatory and Immunomodulatory Potential of the Novel PDE4 Inhibitor Roflumilast In Vitro." J. Pharm. Exp. Therap., 297:267-279, 2001.

RESPONSE

Applicants respectfully traverse this rejection. The references of record do not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The Examiner has failed to establish a *prima facie* case of obviousness against the presently rejected claims.

For the sake of brevity, the arguments set forth above in section 1 are incorporated herewith as they pertain to the teachings of the Rennard, Ghebre-Sellassie, and Remington references, and including the teaching away of Chiou. The additional Hatzelmann reference does not remedy the deficient teachings of the aforementioned combination of references and, thus, cannot establish a *prima facie* case of obviousness

against the presently rejected claims.

The Examiner asserts that "Hatzelmann teaches that roflumilast and its N-oxide are both useful as pharmaceutical agents and as PDE4 inhibitors." The Hatzelmann reference relates to roflumilast and roflumilast N-oxide. Hatzelmann does not teach or suggest using an aqueous PVP to prepare a low solubility drug formulation.

Thus, a person of ordinary skill would not be motivated, upon reading the Hatzelmann reference, to combine it with the teachings of the other references to obtain a process for producing a dosage form of a low soluble drug comprising granulation by spraying aqueous PVP.

As such, applicants respectfully request that the Examiner reconsider and withdraw the rejection.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that this application is in condition for allowance, or reduces the number of issues for appeal. Accordingly, Applicants respectfully request entry of the amendment, reconsideration and withdrawal of the rejections, and allowance of the claims. An early and favorable action is earnestly solicited.

If the Examiner has any questions or wishes to discuss this matter, the Examiner is welcomed to telephone the undersigned attorney.

Respectfully submitted,

NATH & ASSOCIATES PLLC

Date: July 25, 2008

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Attachments: Appendix of Amended Claims (9 pages)